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Alzheimer's Disease

MEDICINE FOR THE LAYMAN

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Foreword

Americans continue to demand a greater role in deciding issues that affect their health. Increased health awareness and the convincing evidence linking lifestyle, risk factors, and specific diseases have accelerated our need to know.

The Clinical Center, recognizing the importance of providing information to facilitate intelligent decisions on health issues, created a unique lecture series featuring physician scientists working at the frontiers of biomedical research at the National Institutes of Health.

The Medicine for the Layman series has provided an opportunity for thousands of people to learn more about how their bodies work and what they can do to maintain or improve their health.

This publication is one of several adapted from the series. It is our sincere hope that you will find this material interesting and enlightening.

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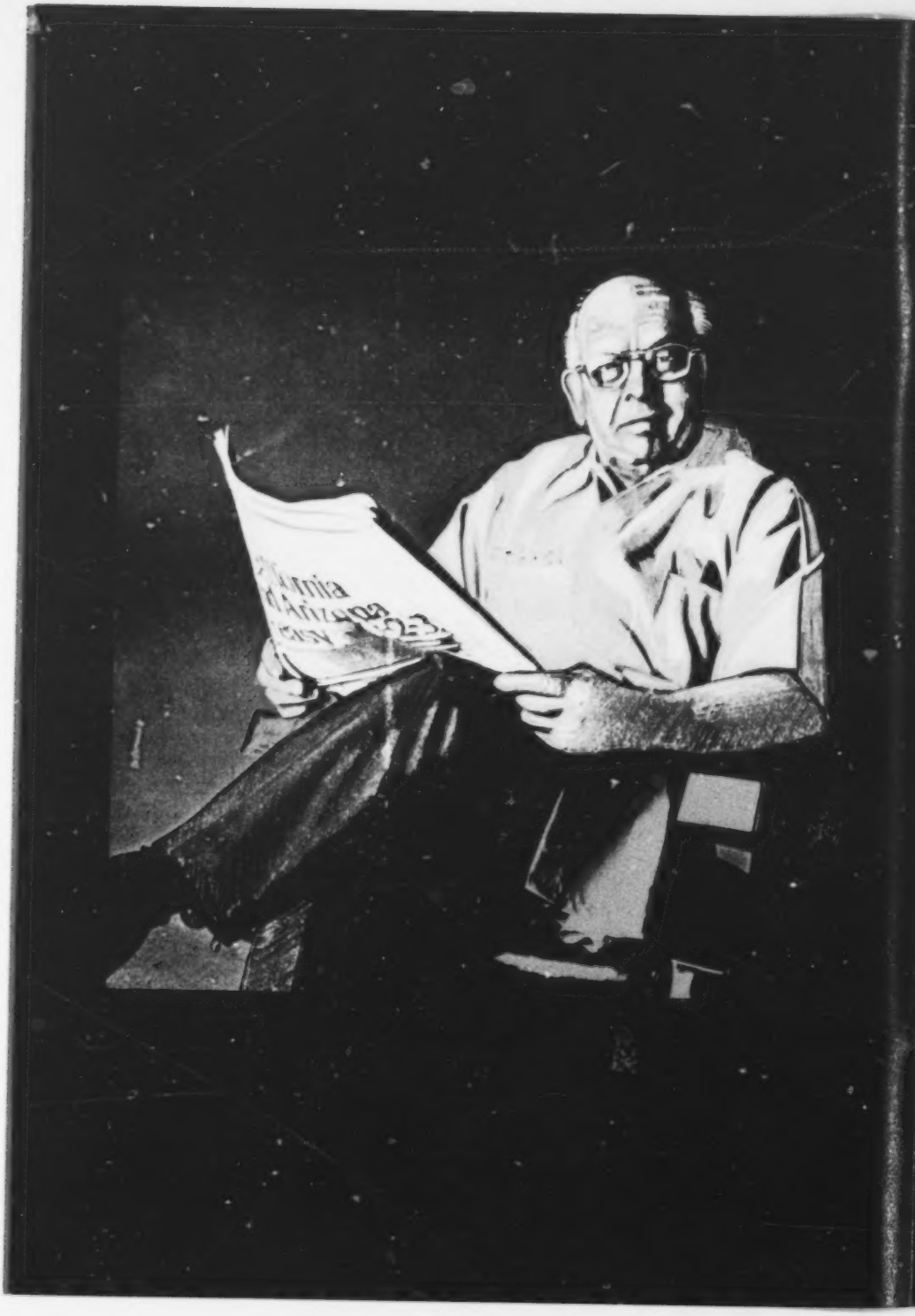
MEDICINE FOR THE LAYMAN



Alzheimer's Disease

All of us, at one time or another, have forgotten things and have had occasional difficulty with memory. This is very different from dementia or Alzheimer's Disease. There is no broad "brushstroke" that gradually sweeps from forgetfulness to this disease. Rather, Alzheimer's Disease is an illness associated with definite abnormalities of the brain that can be seen through diagnostic radiology.

Alzheimer's Disease has a unique pathology, with a characteristic breakdown or deterioration of cells throughout the brain. Portions of the brain are damaged and collect clumps or deposits of dead cells called plaque, and nerve fibers become tangled. Moreover, Alzheimer's Disease engenders far more than loss of memory, the chief symptom of the illness. Alzheimer's patients have difficulty with their usual daily activities. They have trouble socializing and may undergo behavioral changes unlike their usual personality. In short, this disease, which primarily affects people 65 or older, becomes progressively worse and encompasses far more than just loss of memory. The disease primarily affects relatively recent memories; childhood memories, such as nursery rhymes and old songs may remain intact.

There is as yet no cure for Alzheimer's Disease. A number of therapies exist, however, that can temporarily improve the quality of life of patients. Promising tools for early diagnosis and treatment of this progressive illness are on the horizon. Because Alzheimer's Disease usually targets the rapidly rising population of people 65 or older, incidence of the illness may double or even triple during the next 30 years. It is important to realize that the vast majority of people over 65 do not develop the disease.

The special nature of Alzheimer's Disease is important to note because there exists an "Alzheimer's phobia." People say to their doctor, "I'm forgetting things. Please treat my

Alzheimer's Disease." In fact, these are usually healthy people who have no symptoms of the illness nor are they at risk for developing it.

History of the Disease

What is Alzheimer's Disease? How long have we known about it? Although people have called this disorder by different names, this disease has been around for centuries. Written descriptions date back to the ancient Greeks. It was not until 1906, however, that the German pathologist Louis Alzheimer first saw the characteristic plaques and nerve tangles in autopsy tissue from people who had suffered from dementia. Alzheimer correlated these brain abnormalities with the memory problems of his patients.

Alzheimer's Disease cuts across all cultures and populations. There are similar percentages of people with the illness around the world. Because there is a greater likelihood of developing the disease with increasing age, and because the older population of western countries, particularly the U.S., is growing faster than any other age group, more and more people have the illness. In the last few years, the number of people with Alzheimer's has risen dramatically in the U.S. Unfortunately, this increase is expected to continue.

About one out of every 20 people over the age of 65 suffers from some form of dementia. Alzheimer's Disease, a particular type of dementia, accounts for about half of these cases. The older a person gets, the more likely he or she is to develop the disease. The risk for Alzheimer's increases about 1 percent for each year over 65. By the age of 85, a person's chance of developing Alzheimer's has increased from one chance in 20 to one chance in five.

Myths about Alzheimer's and the Elderly

There are a number of myths and unfounded fears associated with this disease, and with the elderly in general. These myths should be dispelled before delving into detailed descriptions of Alzheimer's, and possibilities for its diagnosis and treatment.

The first myth is that most people over the age of 65 are in nursing homes. This is just not true. In fact, the number, once again, is that one in 20 of this age group is in a special home. Alternatively, 95 percent of people over 65 are not in special homes, and most are living in a somewhat independent or totally independent manner.

A related myth is that senility or some type of brain dysfunction is to be expected in people 65 or older. Not so. As indicated, dementia does increase with age, but the same faulty reasoning might lead us to incorrectly conclude that most women in their 20s and 30s are pregnant, just because this is the most likely age group to have a baby. Theories indicate that age is not the only risk factor for Alzheimer's. In addition to age, there is some susceptibility, perhaps to a toxin, that may trigger development of the disease.

Another myth is that retirement and inactivity can somehow cause Alzheimer's Disease. Actually, the converse is true. People with Alzheimer's Disease may have to stop working due to the severity of the illness. Inactivity is sometimes the result of this disease, but it is never the cause.

A different type of misconception, one actually based on some limited scientific data, is that excess intake of aluminum triggers Alzheimer's Disease. About a decade ago, scientists observed a slight increase in aluminum concentration in brain tissue of Alzheimer's patients. Researchers now believe that the excess aluminum found in the plaques and nerve tangles of brain tissue from affected patients is a secondary phenomenon, a result of the illness, not a cause. Moreover, aluminum is a common element on the surface of the earth, and it may not be surprising that it is found in body tissue.

A final myth about Alzheimer's is that most people with the illness are automatically better off in a nursing home. In fact, there are many thousands of patients around

the country, particularly those in the early stages of the disease, who are not in nursing homes and who are cared for by their families. As the illness progresses, understanding the capability for interaction between the family and the patient is extremely important in determining the need for a nursing home. No one can predict when the transfer will be necessary or even if it is necessary. That is up to the family and the patient.

Symptoms

Physicians divide Alzheimer's Disease into three stages—early, middle, and later. There are a number of characteristic symptoms associated with each stage. In the early stages, there are some differences among the sexes that may primarily reflect traditional roles for elderly men and women and may not be true 20 or 30 years from now. For women, some of the earliest signs of the disorder may be difficulty in trying a new recipe, playing cards, keeping house, and making shopping lists. Early signs of the disease for males often include difficulty paying bills and using maps, especially if they are traveling to a new place.

If they are still working, both men and women will experience problems functioning on the job and often are

forced into early retirement. Both sexes also begin to have difficulty driving, and eventually it becomes necessary for their safety and for others on the road to take away their driver's license. The inability to drive can be devastating, particularly in the U.S., which places a high premium on owning and driving a car. Alzheimer's patients also have trouble socializing and reading, and often forget names. We have to be careful with assessing some of these early symptoms, because all of us lose an occasional shopping list or forget something in our day-to-day lives. Careful judgement is needed not to over-interpret what is normal forgetfulness.

As we go on to the more middle symptoms of the illness, it becomes clear that the patient is suffering from something much more serious than occasional absent-mindedness. The transition is subtle as the illness progresses. But patients in the middle stage will have more difficulty speaking. You may understand the gist of what they are saying, but not the detailed facts. Or it may take an Alzheimer's patient five minutes to explain a simple matter. Patients have difficulty in following directions, and perhaps most distressing to families, erratic changes in mood and other behavioral problems develop. These become worse in the later stages of the disease.

At this point, the pattern of daily living for the patient has altered radically. Someone who was a high-functioning executive has long since retired. There is a great deal of confusion, fright, and frustration on the part of an Alzheimer's patient as he loses his capabilities. An analogy can make that point more clearly. If you've ever been stopped by a policeman for speeding or some other misdemeanor, it can be quite frustrating when the policeman says, "Your license, please," and you get this sinking feeling that you just can't find it. You have your license with you somewhere, but you look in your wallet and you just can't find it. You feel great pressure to find the license, you feel you know where it is, but your mind goes blank. This is how an Alzheimer's patient feels almost all the time. They feel pressured, as though you are putting them under a spotlight and they have to answer a question immediately.

They get flustered. Just like the person searching for his license, the answer is often on the tip of his tongue, but he just can't say it.

This kind of frustration often leads to behavioral symptoms. Imagine how it feels to realize that you once knew the answer to something, but you no longer do. Alzheimer's patients often get clinically depressed. They feel angry, withdrawn, and paranoid. Related behavioral symptoms include sleeplessness and repetitive questioning; the patient may ask a spouse or partner "Did we eat breakfast?" six or seven times, or even eat six or seven breakfasts, because they cannot remember.

Some of these symptoms are identical to those observed in patients who have anxiety and depression. In fact, some drugs and other therapies that help these depressed patients may also help Alzheimer's patients, although the basic memory loss cannot be restored. With proper medical supervision, such drugs as tricyclic antidepressants or such anti-anxiety agents as Valium can calm Alzheimer's patients and relieve sleeplessness. A class of drugs known as narcoleptics can sometimes relieve the hallucinations and agitation of Alzheimer's patients.

Symptoms associated with the later stages of Alzheimer's Disease are the ones most people think about in relation to this illness. Certainly, this is the most severe stage of the disorder; the stage at which people are often placed in a nursing home. Patients have become much more restless, and they can no longer feed or care for themselves. Perhaps most insidiously, once immaculately dressed men or women can no longer remember to clean or dress themselves. They appear disheveled, wearing the same clothes to bed as they wear during the day, and they fight with their spouse or caretaker about changing clothes.

Diagnosing the Disease

Diagnosing Alzheimer's Disease in its later stages is not difficult. But how do doctors make the initial determination in the early stages of the illness? Currently, there is no method that is 100 percent accurate. The only way to definitively diagnose Alzheimer's Disease is to examine the brain under a microscope after death (perform an autopsy), and to look for the telltale plaques and neurofibrillary tangles.

We do not yet know the underlying mechanism that causes these brain cell abnormalities in Alzheimer's Disease. We do know that the damage caused by Alzheimer's is scattered throughout the brain, rather than concentrated in any particular region.

There are a few diagnostic tools that can be used in patients to help determine if they have the disease. Eventually, the ability to obtain an early diagnosis may save or prolong the lives of patients. One tool is the biopsy, the surgical removal of a small piece of brian tissue to diagnose the illness. Only a few physicians in the U.S. and abroad perform the procedure, simply because it is so invasive. Another, more familiar tool is the CT scan, a three-dimensional X-ray of the brain. The CT scan image shows that the solid portion of the brain of Alzheimer's patients, the grey matter, has shrunk and the spaces in between, filled with ventricular fluid, have enlarged. However, not all

people with Alzheimer's Disease have these kinds of changes, so the diagnosis by CT scan is not 100 percent reliable.

Another test under development involves sampling the cerebrospinal fluid through a procedure called a spinal tap or lumbar puncture. Because the brain and the spinal cord are connected, fluid that bathes the brain eventually is collected in a small sac at the base of the spine. Extracting and analyzing the fluid from this sac may help diagnose the disease. Recently, researchers found an abnormal protein that is present in the brains of Alzheimer's patients, which may be present in the cerebrospinal fluid. If so, the spinal tap may become an accurate and less invasive method for diagnosing Alzheimer's Disease.

Other types of diagnostic tests simply rule out the possibility of other diseases. A thyroid gland abnormality, an infection, anemia, or cancer that has spread to the brain can mimic some of the symptoms of Alzheimer's Disease. A stroke that damages the brain can also have some similarities with Alzheimer's Disease, but an X-ray image reveals that the damage is at specific sites and often associated with such physical symptoms as the dragging of a foot or partial facial paralysis. Severe alcoholism also is associated with memory disturbance and dementia, as is the type of repeated head injury encountered by a professional fighter. Parkinson's Disease often is mistaken for Alzheimer's. Perhaps most significantly, severe depression also has symptoms akin to Alzheimer's Disease.

The inclusion of depression is important, not because it is the most common illness that shows similarities to Alzheimer's, but because it is one of the only illnesses on the above list that can be treated and reversed. Depression and Alzheimer's may at first appear quite different; we associate the former with a person feeling extremely sad and hopeless, while the latter might be exemplified by a demented patient who can't remember what day it is. In fact, people over the age of 65 who are depressed often complain of loss of memory. So to differentiate between depression, a curable disease, and Alzheimer's, a currently incurable illness, is both critical and difficult.

Possible Causes

People have searched for many causes of Alzheimer's Disease. Because we know that some kinds of dementia are transmitted by a virus—a form of dementia is associated with the AIDS virus, for example—researchers have looked for a viral cause of Alzheimer's Disease. Negating the viral theory, however, is the thousands of unsuccessful laboratory attempts to transmit Alzheimer's Disease from damaged brain tissue to healthy tissue. Such transmission or infection should be possible if a virus that causes the disease exists. Other negative evidence comes from the fact that spouses of Alzheimer's patients, although they live intimately with their affected partner and would come into contact with any infectious agent causing the disease, have no increased incidence of developing Alzheimer's Disease than the general public.

Genetic Links

Recently, researchers have found several genetic links to Alzheimer's Disease. One example is the observation that in some families, five or six people in generation after generation develop Alzheimer's. In such a family, a healthy person is at increased risk for developing the disease, and at a younger age than the average.

Perhaps the most exciting genetic link is the recently discovered connection between Alzheimer's Disease and Downs Syndrome. Downs Syndrome is a birth defect associated with a duplication of chromosome 21 that causes mental retardation and a shortened life span. Although young people who have Downs are severely impaired, they can learn many tasks and function in a sheltered environment. Researchers have learned that as these youngsters grow up and enter their third and fourth decade of life, they often develop memory problems or dementia similar to Alzheimer's Disease. Physicians have examined the brains of some of these older Downs patients after their death and have found many of the plaques and neurofibrillary tangles characteristic of Alzheimer's Disease. Moreover, in families with a history of Alzheimer's Disease,

preliminary studies indicate a higher-than-normal incidence of Downs syndrome.

The Downs-Alzheimer's link is exciting because it suggests there may be an abnormality for Alzheimer's Disease similar to the abnormality that causes Downs Syndrome. Identifying a possible genetic mutation for Alzheimer's gives hope of one day altering that mutation to prevent the disease from occurring. Chromosomal studies are one of the most active areas of research on Alzheimer's Disease.

Alzheimer's researchers interested in genetics have studied identical twins. Scientists reason that if a gene appears to code for Alzheimer's Disease in one twin, it should also code for the disease in the other. In fact, if one of a pair of identical twins develops Alzheimer's, there is a greater than 50 percent chance that the other twin will eventually develop the illness. However, identical twins do not usually get the disease at the same time—there is usually

a separation of 10 to 12 years—nor does the disease run a similar course in both individuals. And there are many cases where one twin leads a perfectly healthy life and never develops the disease. Scientists interpret these findings to mean that in addition to hereditary factors, there must be some environmental influences—perhaps diet, life style, or susceptibility to some toxin—that play a role in causing Alzheimer's Disease. These as yet unknown environmental factors are believed to interact with the genetic code we are given at birth to make us more or less susceptible to Alzheimer's.

Acetylcholine: Another Possible Link

Acetylcholine is one of the best known chemical messengers in the brain, bridging the gap between adjacent nerve cells so that messages can be transmitted from one neuron to the next. More significantly, the activity of acetylcholine is associated with memory. If this natural drug is somehow blocked or reduced, there is a corresponding loss in ability to remember. Researchers have found that in addition to destruction of nerve cells in the brain, Alzheimer's Disease also causes a reduction in acetylcholine. In the hope of restoring at least some memory to Alzheimer's patients, scientists are searching for drugs that will replenish the reduced supply of acetylcholine and perhaps other chemical messengers in the brain. Recently, a drug called THA has shown some positive effects in increasing acetylcholine. The drug is still undergoing clinical trials. Because THA acts only on acetylcholine, and not on other chemical messengers that may be involved in memory, it is unlikely that this drug alone can reverse Alzheimer's Disease. But at this point it is one of the most promising experimental drugs available.

Other Therapies

Other therapies can make Alzheimer's patients more comfortable and more alert, although they cannot reverse the underlying memory loss. The drug Hydergine has some therapeutic value for Alzheimer's patients. Stimulants such as Dexedrine may help. Antidepressant drugs, as previously mentioned, can reduce the depression, anxiety and paranoia that is often associated with the illness.

Drugs are not the only therapy available. Having a pet, for example, can be a vital lifeline for an Alzheimer's patient who may feel isolated. In the early stages of the disease, the ability to take care of a pet can help make the patient feel needed and useful. Another way of improving the quality of life of an Alzheimer's patient is through music. Because Alzheimer's Disease primarily affects new memories and tends to leave old remembrances intact, the patient is likely to remember favorite tunes. Most people with Alzheimer's Disease still have the capacity to sing and remember songs they learned in childhood. They may no longer be able to play the piano, but they have great memories of past songs. Music taps these memories. This is important, because it allows Alzheimer's patients to socialize and be drawn out of their isolation.

Volunteering to play with young children in daycare centers is another way for some patients to socialize and feel needed, and to be part of a vital activity. Another way of reaching an Alzheimer's patient is through exercise. People tend to ignore the fact that an Alzheimer's patient may be physically well; although an individual may be unable to keep score, playing games is still possible. An Alzheimer's patient may be able to walk 5 to 10 miles a day, but will need supervision.

A caretaker can provide several items that can aid an Alzheimer's patient in remembering things. Putting up a calendar is a quick and easy reference for patients to verify the day and year. Lists of daily tasks may give patients an extra feeling of security and purpose. Color-coded labels, such as a rainbow or heart, can help remind a patient where a closet or bathroom is and may be easier to remember than a written note.

Recognition of the Caretaker

Before discussing progress in the treatment of Alzheimer's Disease, let us acknowledge the unsung hero of this devastating illness—the caretaker. It could be a spouse, son, daughter, or other person. These people cope with tremendous stress and are often on-call 24 hours a day. In addition, they deal with the terrible ordeal of watching the patient die twice; first is the death of the patient's intellectual abilities, and finally, the death of the body. The caretaker must make important decisions alone, and are themselves prone to anxiety and depression. Caretakers need to take care of themselves, to take a break when possible, and make sure that there are other people supporting their effort to maintain the ill person at home. Family members need tremendous support in trying to determine when and if the patient should be placed in a nursing home.

Prognosis for the Future

We know that Alzheimer's Disease is more likely than ever to be an illness associated with aging. The hope is that with new techniques to make an early diagnosis, effective treatments for memory loss will have the greatest possible impact. Such treatments do not now exist. With new genetic clues appearing almost monthly, there is hope of developing new drugs and other therapies. Drugs now in clinical trials and animal models of Alzheimer's Disease are helping us to understand more about the illness. Finally, taking a cue from experimental surgery to transplant cells in the brains of Parkinson's Disease patients, new research may suggest a type of brain surgery to correct or at least slow down the loss of memory in Alzheimer's patients.

Questions and Answers

Q. Does any new imaging modality, such as MRI or PET scanning show promise in treating Alzheimer's Disease?

A. Although these imaging techniques are not yet linked to therapy, they are useful supplements to the CT scan. The techniques are helping us understand the exact areas of the brain that are damaged. The PET scan in particular has tremendous potential because one can label individual chemicals and track where they go in the brain. PET, however, is very expensive, and is not generally available.

Q. Is there an age, say 85 or 95, by which if we haven't yet developed Alzheimer's Disease, we can be assured of never getting the illness?

A. Unfortunately, no. The risk of developing the disease increases with age.

Q. If you have a relative at home who has both depression and evidence of dementia, how do you distinguish between the two disorders?

A. There is no diagnostic test. The patient should be examined carefully by a physician who is experienced in treating both populations. There are patients with dementia who also have severe depression, and we can help them by treating their depression. After successful treatment though, they will still have the same baseline dementia.

Q. How quickly do people pass through the three stages (early, middle, later) of Alzheimer's Disease?

A. As people are being diagnosed earlier, our collective consciousness about the illness is being raised, but the staging is unclear. We now think the total illness, from the

time of diagnosis until death, is about 12 to 18 years. A patient might, therefore, spend three or four years in each of the stages, but that is a very approximate guidepost.

Q. Is it common for an Alzheimer's patient to deny their problem?

A. It is very common. About 80 percent of patients deny their illness to begin with or try to cover it up by writing secret lists to themselves or pretending they know someone when, in fact, they can't recall the name. Whereas a depressed person will point out their difficulties, almost ad nauseam, the Alzheimer's patient often goes to the opposite extreme to avoid acknowledging their problems, even when they are obvious to others.

Q. Could the depression experienced by an Alzheimer's patient be caused by their awareness of the stress they put on caregivers?

A. That is a complex question. We think that part of the depression might be caused by the patient picking up on the spouse's or caregiver's feelings. Patients in the early stages of Alzheimer's Disease, who are most capable of recognizing the stress they may place on a caregiver, are not generally more depressed than patients in the later stages of the illness. We believe that the depression has a large biological component. The plaques and tangles of Alzheimer's Disease affect the centers of emotion in the brain, and may cause depression. To summarize, the depression felt by patients is probably a mix of both psychosocial factors and biological factors.

Q. Do younger people ever develop Alzheimer's Disease?

A. The youngest person reported to have the disease was age 28. The youngest person whom we have treated was 42 when she came to our ward. Only a small minority of Alzheimer's patients are under 50 years of age. The vast majority are over 65, and the average age is 70. Alzheimer's Disease that runs in families tends to strike at an earlier age, however.

Q. Why is it that aluminum seems to be concentrated in the brain of Alzheimer's patients?

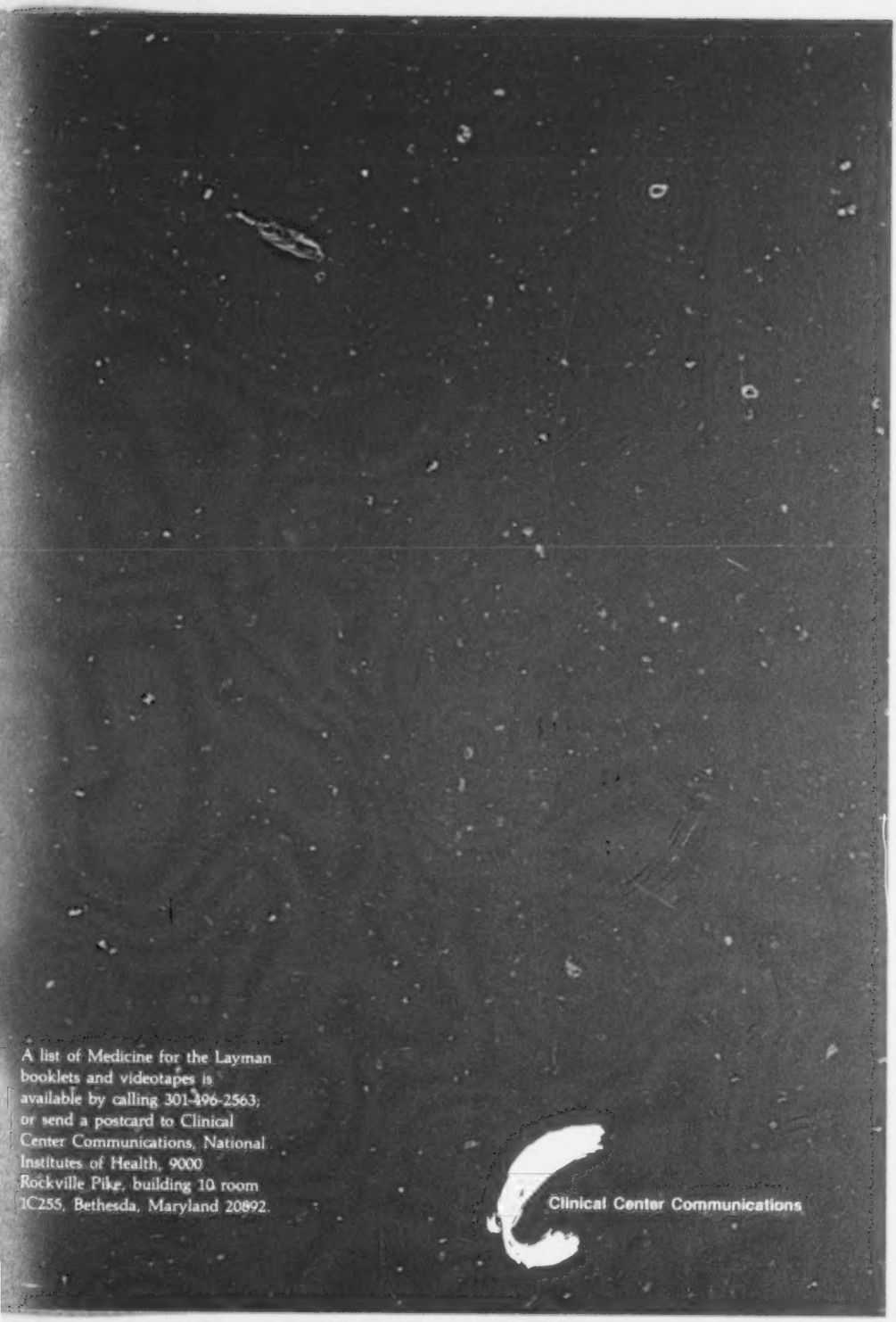
A. That has been a hotly debated issue for ten years. At a recent medical meeting on the subject, research scientists were unable to find a satisfactory answer. The most straightforward explanation may be that once the brain is damaged, it acts in some ways like a drain or sieve. Some things that pass through are more likely to be collected. Aluminum will not be the only element found in increased concentration in the brain of these patients, but it is the first.

Q. If the damage caused by Alzheimer's Disease is scattered among all portions of the brain, why are motor abilities (walking, muscle coordination) unaffected?

A. One theory is that motor functions are more primitive so that they are coded in more than one part of the brain; for example in the brain stem, the lower part of the brain, which is unaffected by Alzheimer's Disease. Alzheimer's Disease affects the gray matter in the cortex or mantle of the brain; this is the part that determines the ability to use cognition and makes humans different from the lower animals.

Q. Have there been any studies of the brain wave activities of Alzheimer's patients and how have they differed?

A. Researchers have found a decrease in the normal thinking wave pattern, the alpha wave, in the EEG of Alzheimer's patients. The decrease is more pronounced with the severity of the illness.



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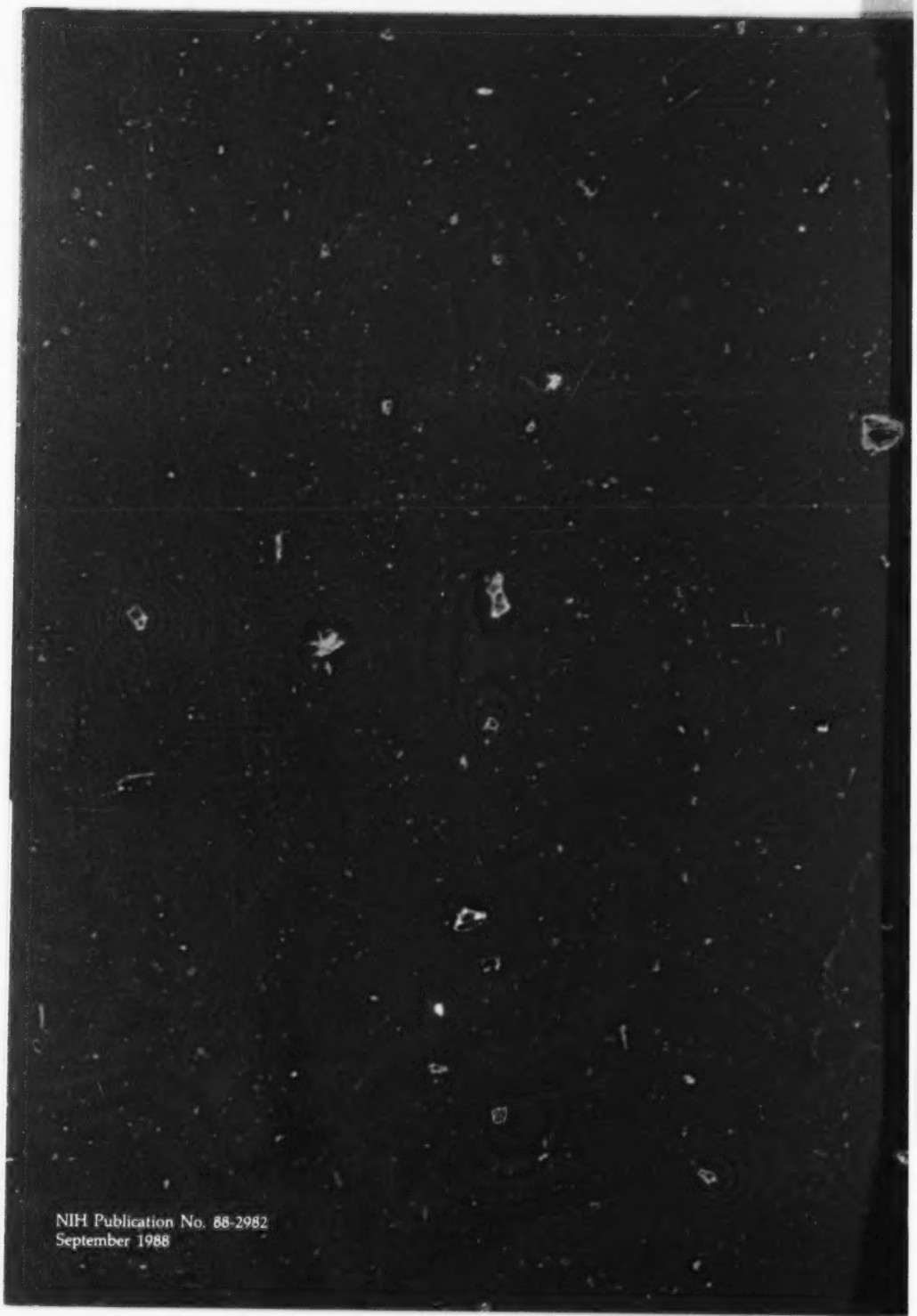

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